APPENDIX A

Genome

INSIDE

Issue 3 November 03

DUKE Institute For Genome Sciences & Policy

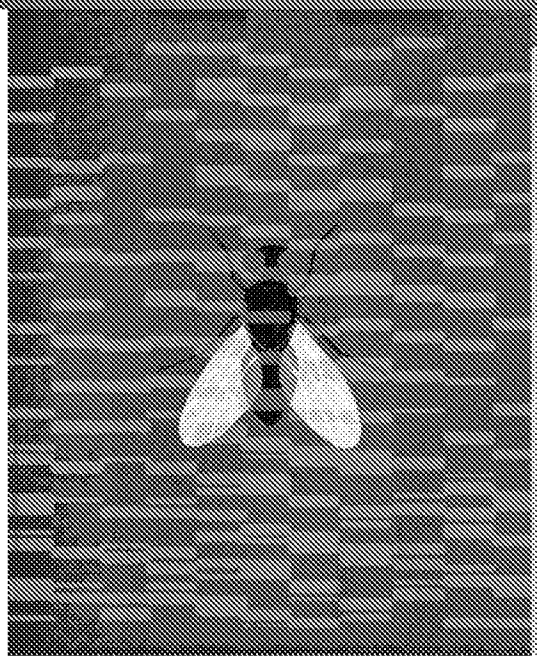
Duke Biology Embraces Genomics

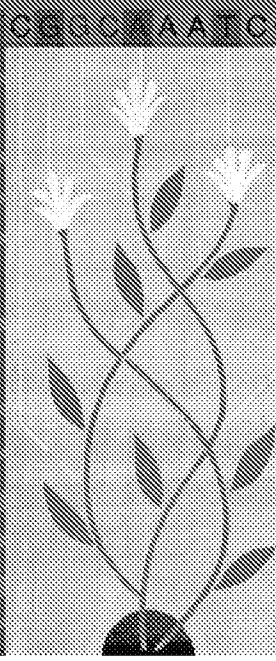
Benfey Expands Department's Range of Organisms and Approaches

Even though he's only been here a year, Paul Kramer Professor of Biology and Duke Biology Chair Philip Benfey has no illusions about the impact of genomics on university biology departments. In his view, the advent of genomics has already set in motion a natural selection process that will soon bring harsh realities to many in biology—if it hasn't already. "I believe we're rapidly moving toward a time when there will be a bi-modal distribution of biology departments," he says. "And what's driving that is primarily genomics-related." He cites the equipment necessary for genome research as being well beyond the start-up budgets of most junior faculty. In addition, even when faculty can afford such equipment, Benfey notes how rapidly those machines become obsolete. "Consequently," he says, "the haves and the have-nots are getting separated. The rich get richer in this climate."

Another factor dividing biology departments is computation. Benfey believes that, moving forward, successful integration of sophisticated computational approaches into the work of biologists----much like what the Center for Bioinformatics and Computational Biology is attempting to do--will be an absolute necessity. In his view, should biologists fail to make high-level computation part of what they do----or at least be conversant in the language of computation—they will find themselves on the outside looking in.

And now the good news: "I think Duke is well-placed in both of those areas," Benfey says. In fact, he sees Duke as being exceptional in its embrace of both genomics and computational biology. He notes that few biology departments have combined the two and have the resources to make a sustained commitment to integrating both fields.





Ecology and Evolution Join the Party

In some cases, incorporating genome sciences and bioinformatics is a seamless transition, particularly in the area of "functional biology," the branch that encompasses cellular, molecular, developmental and physiological approaches. Functional biologists have already been utilizing genomic tools for a number of years. For the other two major branches of biology----ecology

Biology and Genomics *(continued on pg 2)* >

Message from the Director

One of the transforming qualities of the Genome Revolution is that it promises to affect virtually every facet of human activity: science and health, agriculture, economic and social policy, even the arts. If we truly believe this, shouldn't our country's campuses anticipate the increasing influence of the genome sciences? Unfortunately, we know that most don't, for a variety of reasons: lack of resources, lack of interdisciplinary traditions, intransigent faculty, and probably many others.

In this month's lead article, Philip Benfey demonstrates how the Biology Department at Duke has sidestepped these pitfalls and created an environment that has embraced genomics and integrated it seamlessly into all areas of biological research. I am heartened by the knowledge that right down the hill live a myriad of potential collaborators, sounding boards and novel perspectives on the genome. If the IGSF is doing its job right, the Biology Department will feel the same way about us.

Clearly, Duke Biology is a living, breathing example of how genomics is so much more than "just medicine". And if we delve a bit deeper into Trinity College, we find that other departments—English, Psychology, Philosophy, African and African-American Studies, just to name a few—are also actively interested in the Genome Revolution and the implications of what we do. The same sense is mirrored in other schools around campus, and several novel genome-related linkages between schools will be highlighted in upcoming issues of *GenomeLIFE*.

I can hear some scientists and students wondering why they should care. I would contend that when an English professor like Priscilla Wald starts asking questions about public perceptions of genetics (as presented in this issue), this is cause for celebration, not consternation. It represents an opportunity to engage an entirely different set of scholars than those who think about the genome at other institutions. And while genome scientists may have quite different perspectives from some sociologists about, say, the biological significance of race, those differences will never be explored in a meaningful way without interdisciplinary discussion. The October 31 Symposium on Race, Genetics and Human Diversity (see page 6) is an example of exactly the type of forum needed to foster that dialogue.

In large part, the IGSF exists to build these types of bridges on campus — between the natural sciences and the humanities, engineers and scholars of divinity or the environment, lawyers and business leaders, policy experts and nurses. By doing so, we will also tap into a critical constituency and resource: Duke undergraduate, graduate and professional students. They will decide how the genome sciences are used and perceived in the future, and ultimately, it is they who will shape the evolution of the Genome Revolution. ❧

Huntington F. Willard, Director

Biology and Genomics (continued)

and evolution—the process of integrating genomics has been slower.

Within ecology, Rob Jackson, Director of Duke's Program in Ecology, provides an example of how genomics can be a useful tool. His lab is using microarrays to look at changes in gene expression in pine needles in order to determine what effect elevated carbon dioxide exerts on ecosystems. "Rob's group is still in the very early stages of this work," Benfey points out, "which has all sorts of difficulties that those who work on model systems don't have to face. For example, they have to make their own microarrays with 3000-4000 cDNAs on them. Then they have to account for the variability one finds in a wild system. But I say more power to them."

In the evolutionary group, Associate Professor Greg Wray is conducting population-wide analyses of genes' promoter regions in order to look at how a binding site can change. Wray has shown that the promoter region possesses extraordinary variability from individual to individual. Benfey notes that Wray's team is making inroads into mapping transcriptional networks in the sea urchin. "This is taking systems biology to a population level," he says.

Genomics practitioners among the Duke department's functional group include Dave McClay, who, like Greg Wray, is utilizing the sea urchin as a model organism. McClay's interest, along with that of collaborator Eric Davidson at Cal Tech, is in elucidating the components of networks that regulate genomes. And just across the hall from Benfey is Xinnian Dong, who is investigating plant-pathogen interactions using microarrays.

Benfey's own work, too, relies heavily on genomics. Recently, his team had a paper accepted by *Science* that will likely be the first published expression map of a complete plant or animal organ at a near-cellular level of resolution. That organ is the root of Arabidopsis, a small flowering member of the mustard (Brassicaceae) family that is widely used as a model organism in plant biology.

Looking ahead, Benfey wants to focus on mapping out transcriptional networks in Arabidopsis, much as McClay is doing in the sea urchin. This interest has also induced him to pull together groups from across campus who are working on similar questions. The result is the Biological Networks Group, a collection of systems engineers from the Pratt School of Engineering, biologists from both Biology and the Medical School, and computer scientists. Benfey explains, "It's very common now for life scientists to say, 'We're taking a systems engineering view of biology.' But very few of those people have ever talked to a systems engineer. I thought it would be really interesting to get some systems engineers and see, well, what do they actually have to say about biological inputs and outputs?"

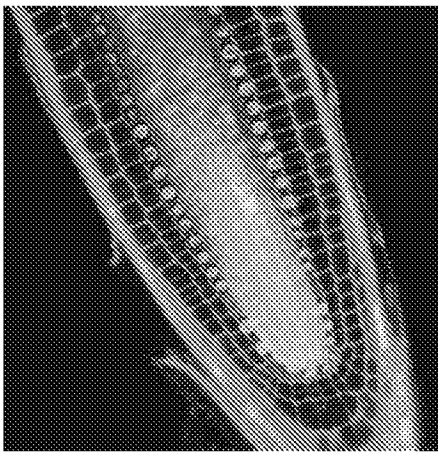
Model Behavior

Another source of pride for Benfey is his faculty's willingness to pursue avenues of research well off the beaten path. In particular, he points to the fact that some two-thirds of Duke Biology faculty members are utilizing "non-model" organisms. In other words, they are studying biology in species for which there is not an abundance of molecular resources such as fully sequenced genomes. Rob Jackson's microarray study of pine needles is one example. Another is Associate Professor John Willis' studies of speciation in the monkey flower genus Mimulus. Recently, Willis' group at Duke was chosen to lead a consortium of six universities in a $5 million project to investigate what separates species at the molecular level.

For Benfey, bringing the advantages of model systems (e.g., human, mice, yeast, Drosophila, zebrafish, Arabidopsis) to non-model systems remains a challenge, but one that is becoming increasingly tractable, in part through novel methods such as RNA interference that can modify gene activity and in part because mapping and sequencing have become a lot cheaper. "A lot of high-throughput technology can now be applied to any organism," he says. "To my mind, these approaches are the kinds of things that will differentiate the places that are doing exciting research from those that aren't. Of course, that doesn't mean that everybody should start doing genomics just for genomics' sake. Rather, my point is that if a genomic approach can bring one a strategic advantage or get one to the answer faster, then we should be aiding people in that approach as much as possible."

Within the department, Benfey has set up mechanisms to do exactly that. First, he has established a committee whose job it is to know exactly what technical resources are available in Biology and make them known to everyone. Benfey knows that it may sound trivial to some, but in a department as big and decentralized as Duke's, he views this type of cataloguing as a necessity. "In many places," says Benfey, "nobody talks to each other, nobody knows what's there. We can't afford to do that anymore. We need for people to know what we have."

But knowing what's available is not enough, says Benfey. He believes that faculty----not to mention postdocs and students----must have support and guidance if they are to succeed in using unfamiliar techniques. "We need to help them at every step," he says. "Everywhere from experimental design through execution to analysis." The prototype for this approach is the department's Model Systems Genomics Center (MSGC), which is complementary to the IGSP's Center for Models of Human Disease. Theoretically, anyone in the state can come to the MSGC with a scientific problem to be addressed in Drosophila. Benfey cites the expertise of MSGC Director Eric Spana, a former group leader at agrochemical giant Syngenta with postdoctoral experience. "He will walk people through the process from start to finish." Benfey believes that the use of experimental core facilities like the MSGC will only become more widespread in the future. "I think it's a particularly important resource for biologists who may have less experience with certain techniques."



A root of the model plant Arabidopsis which contains a fluorescently tagged protein that moves from the inner tissue to surrounding cells. Similar fluorescently tagged lines are being used by the Benfey lab to construct global expression profiles at cell-type specific resolution.

United We Stand

For both teaching and research purposes, Benfey appreciates the fact that his department has embraced ecology and evolution at a time when many places are segregating them. From his perspective, the latter approach has tended to create environments where colleagues in split departments don't talk to each other because they are physically separated, they don't see any commonalities, or they simply don't respect one another. Benfey believes that these sorts of cultural divides are exacerbated by differences in funding and departmental politics. Publishing can also create schisms if one sub-discipline is perceived to be inferior.

With regard to support, Benfey points out that funding for tenure-track faculty in his department is strong across the board. As for publishing, Benfey suggests one simply look at the scoreboard. "This department has a rather surprising record," he says. "In the first ten months of this year----if you include papers in press----it has ten papers published in *Science*, *Cell* or *Nature*. We must be doing something right." §

The Medium and the Message:

Q&A with Priscilla Wald, PhD

If she deems the subject matter to be interesting or important, Priscilla Wald is not afraid to venture into the unknown. Never mind that she is a tenured Associate Professor of English who cut her teeth on Melville, Dresser and Gertrude Stein; when genetics come calling, she dove in with abandon. But Wald's interest—sparked by a New York Times article on the bubonic plague and its relationship to HIV-resistance—is not in the science per se (although she did spend a year at Cornell learning genetics). Rather, she is focused on how the culture, rhetoric and ethics of science are transmitted via both popular and science media. One ongoing interest is the concept of the human carrier, from Typhoid Mary to carriers of genetic disease and mitochondrial DNA, detailed in the book she's completing now, *Cultures and Carriers: From Typhoid Mary to African Eve*. This preoccupation led to her more recent fascination with genetics and genomics, which has given rise to a collection of essays in progress, *Clones, Chimeras and Other Creatures of the Biological Revolution: Essays on Genetics and Popular Culture*.

You are an English professor and cultural critic by training. Where did your interest in genetics and genomics come from?

In 1998, I was working on a book on the narrative of emerging diseases, and I came across an interesting feature in *The New York Times* by Gina Kolata on an HIV-resistance gene and whether it might also have been protective against bubonic plague in the 14th century. The article struck me as odd. There were things about it that didn't make sense. So I went and read the original article in the *American Journal of Human Genetics* and, though I could barely understand it, I noticed that there were real discrepancies between the piece I read in the genetics journal and the popular account of it. I then began to notice that the popular account was appearing all over the place, including what I saw as Gina Kolata's errors or mistranslations from the original paper.

The following year I had a leave at the Cornell Society for the Humanities. I was supposed to be finishing the book on emerging diseases, but I got so interested in this piece that I started to educate myself in genetics. All this stuff about the Human Genome Project was just wildly fascinating, like nothing I had ever thought about before—the ethical questions, the cultural representations, all of it. But I also felt that there were problems with the way in which it was getting into the public domain, how these images were circulating through mass media. I felt it was really important to write about it because the science was getting skewed by these representations. And I was concerned that the popular representations would begin to influence how the science was done.

The humanities have a reputation for being pretty hard on the life sciences. Life scientists get bashed for not engaging with the world, for being shills for corporations, for violating various laws of God and nature. Is that true of the humanities and, if so, do the life sciences deserve it?

I think that in some cases there are people in the humanities who work on this material who don't have enough of an understanding of the sciences and might make those generalizations. I think the best people doing this work are not falling into those traps but do have concerns when, for example, the Human Genome Diversity Project allows scientists who have not schooled themselves in social and cultural issues to get involved with issues of race and racism and don't think through the implications or consequences of their work. I think there has to be more communication across these borders and more education, especially at the undergraduate level.

Conversely, science journalism is sometimes perceived to be relentless cheerleading: "Look at these guys curing cancer and splitting the atom!" Is that accurate?

I am not comfortable with that generalization. I've done a lot of work over the past few years specifically on science journalism and that notion of translation I was talking about, that is, how the science gets passed on to the mass media. Science journalism runs the gamut from hyper-

critical to cheerleading. I think it depends on the audience, on the newspaper or magazine, and obviously on the individual writer. You might find cheerleading in a particular newspaper, but another one may be hypercritical.

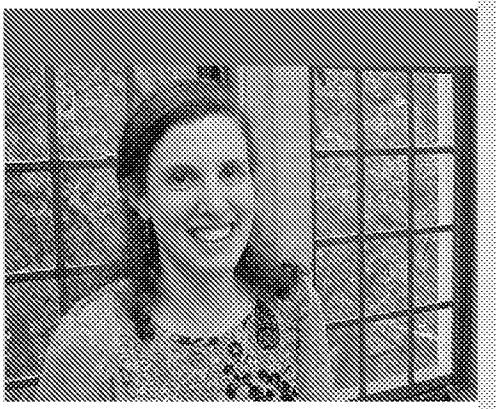
In science journalism, as in all journalism, there are pressures on the writer. One always has to guard against special interests. I am in an enviable position in that I can really write what I believe I see and be pretty much free of outside influence---I don't have to worry about my funding sources. The other problem is, if you're a science journalist, you don't want scientists to stop talking to you. I imagine that would put pressure on a journalist.

You taught a course on religion and genetics in popular culture. Can you describe that experience?

I was particularly interested in putting genetics together with religion because I saw something evolving in popular culture, in films such as "GATTACA" where genetics is counterposed to religion. There's a way in which genetics is seen as godless and anti-religion, which really makes no sense to me. And it's so deeply held: people think of clones as godless or the scientist as "playing God."

How do you think religion and genetics were counterposed in "GATTACA"?

Well, for instance, there's a really interesting scene when the Ethan Hawke character's parents are conceiving him and they're in the back of a car. In voice-over, he narrates that he was conceived the "old-fashioned way." There's a fade-out and then a fade-in on a crucifix that the mother is wearing. As we fade into the birth scene, the voice-over refers to him as a "God child" or "God baby," I can't remember the exact term. But the idea was that because he was not genetically engineered like most people in that society, he was seen as a true "child of God." I think at one point Ethan Hawke's character says, "What possessed my mother to put her faith in God instead of the geneticists I'll never know," or something like that. In the original script for the film, this dichotomy is even more pronounced—the mother is urged to get an abortion because in that society you're not supposed to conceive without a geneticist's supervision.



Priscilla Wald, PhD
Associate Professor of English

So again, there's this real juxtaposition: genetics is looked at as replacing religion. The geneticists are "playing God" and "taking the place of God." That idea felt very odd to me.

Why did it feel odd? Haven't science and religion been sparring for centuries?

I guess I mean that I don't see why people assume that clones wouldn't have souls---things like that. Science and religion may have been at odds in the past, but I think there's a particular sting to genetics that is being reinforced, and largely created, in pop culture today.

I understand that geneticists may be seen as influencing the outcomes of life, but when a doctor practices medicine, he or she is influencing the outcomes of life! It was very interesting to me and I wanted to understand where that image was coming from. And I wanted to explore that in a class with students. ⟫

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Further Reading:

P. Wald, N. Tomes, and L. Lynch, eds. (2002) Culture and Contagion. Special issue of American Literary History, vol. 14 no. 4, Winter 2002.

P. Wald (2000) "Future Perfect: Genes, Grammar and Geography." New Literary History 4: 681-708.

P. Wald (1997) "Cultures and Carriers: 'Typhoid Mary' and the Science of Social Control." Social Text 52-53: 181-214.

Coming in the next issue of

GenomeLIFE:

Environmental Genomics: Not Waiting to Exhale

Duke Undergrads Live the Genome Life

Wilmot James on the End of Race

Biomedical Engineering: Looking for a Few Good Genome Scientists

Center for Genome Technology Gets a Director

Symposium Spotlights Genome Impact on Race and Diversity

GELP Forum Brings Together Science, Medicine and Sociology

On Friday, October 31, scholars, physicians, students and scientists gathered at the John Hope Franklin Center to address questions of race and cultural diversity raised by the emergence of genomics over the last decade. The lead sponsors for the event, entitled "Symposium on Race, Genetics & Human Diversity," were the IGSP Center for Genome Ethics, Law and Policy (GELP) and the Provost Commonfund Group on "Race, Gender, Sexuality and the Cultural Study of Medicine." Co-sponsors included the Women's Studies Program, African and American Studies, and the Mary Lou Williams Center for Black Culture.

Population geneticist and independent biotechnology consultant Spencer Wells led off the proceedings, recounting historical views of human evolutionary history as well as his own work in molecular evolution. Wells' research, based primarily on Y-chromosome data collected from thousands of males representing different geographies and cultures, suggests that humanity shares a single common male ancestor who resided in Africa some 60,000 years ago. Thus, says Wells, this ancestor ("Y-chromosome Adam") lived relatively recently in evolutionary terms. During this same period, something---perhaps the last Ice Age---prompted some humans to leave Africa for more hospitable conditions. Wells speculates that humans may have arrived in the Americas within the last 15,000 years.

Wells concluded by emphasizing that since his data show a very recent common ancestor, racism is not only socially divisive, but scientifically incorrect as well. "We're all closely related," he said. "We're all African cousins."

Dr. Lori Alviso Alvord spoke about her experiences as the first Navajo surgeon and how she reconciles her Navajo upbringing with her life as a doctor steeped in western medicine. Her talk focused on core Navajo beliefs related to genetics, particularly with regard to notions of death, illness and sustainability. For example, she said that many Navajos would probably object to the creation of transgenic animals and plants that breached boundaries between species, based on their views regarding "skinwalkers," Navajo witches who can metamorphose into animals for the purposes of committing evil acts.

Alvord also cited history as an impediment to the acceptance of genetics among Native Americans. "Genetics could be accepted among us," she said. "But it must come in a different package than the one it's come in to date. Indigenous tribes must be at the table when policy decisions regarding genetics are made, and they must derive the benefits from genetics, both in terms of health and financial compensation."

GELP Fellow and Brown University Lecturer Jenny Reardon continued with the theme of genetics and indigenous peoples in her discussion of the history of the Human Genome Diversity Project. The HGDP, originally conceived in 1991 as a way to sample the planet's genomic diversity, became bogged down in controversies regarding how such sampling could be done in ways that were fair to the indigenous peoples under study. Reardon cited a number of hard lessons from the failure of the HGDP to get off the ground. She urged scientists engaged in future similar endeavors not to presume that if a group declines to participate in research, it is simply because they do not understand the research. Reardon also called on scientists to resist the notion that anything they do is inherently good or bad and to question their own understanding of race and diversity.

The final speaker, New York University sociologist Troy Duster, emphasized that the concept of race is itself problematic. Duster pointed out that our categorizations of race are simultaneously arbitrary and deeply embedded. In Duster's view, science itself has not reached a consensus on the matter: on the one hand, he observed, scientists take pains to say that race is not biologically meaningful, while on the other hand, numerous papers have appeared in the last few years citing racial differences in drug response. Duster also spoke at length about the forensic community's rush to embrace DNA evidence, with an inappropriate focus on race, often in the absence of comparative population and environmental data. §

Leon Dunkley, Jr., PhD, Director of the Mary Lou Williams Center for Black Culture and Jocelyn Bailey, Senior Analyst, IT, engage in a lively conversation.

Perioperative Genomics: Anesthesiology Goes Molecular

Schwinn Aims to Bring Genome Science to the "Last Physiology Lab in Medicine"

Think about a distance runner and the changes her body goes through as she picks up speed. Her oxygen consumption increases 15-fold while her exhalation of carbon dioxide rises by a factor of eight. Her heart rate accelerates to nearly 200 beats per minute. Hemoglobin and certain serum enzyme levels rise dramatically. In short, each time she runs she is subjecting her body to acute physiological and biochemical stress.

Surgical patients undergo similar stresses, only more so. The extremes to which a bypass or transplant patient is pushed typically exceed those of even the most stressed athlete. James B. Duke Professor of Anesthesiology, Surgery, and Pharmacology/Cancer Biology Debra Schwinn notes by way of example that the levels of catecholamines----neurotransmitters such as dopamine, norepinephrine and epinephrine (adrenaline) ---- rise even more profoundly during surgery than during exercise. "A runner will double her catecholamine levels when she's pushing the envelope as she might in an Olympic race. But someone having a cardiopulmonary bypass can have a ten-fold increase in catecholamines. Of course, for us, it's all about protecting the patient."

But how? According to Schwinn and a growing contingent of forward-thinking anesthesiologists, the tools of "perioperative genomics" may soon be a standard part of the operating-room arsenal used to ensure patient safety. The idea is simple: since millions of common variants (polymorphisms) in our DNA have been catalogued, it should now be possible to examine specific DNA changes in order to predict negative surgical outcomes such as intraoperative bleeding.

While the concept may be intriguing, it is still in its infancy. A Google search of "perioperative genomics" yields less than two dozen hits (most of those are links to Schwinn and Duke); even a query of the PubMed database generates a mere smattering of scientific references. In part, this is due to the novelty of this approach, but its failure to make much of a splash thus far also reflects a long-standing separation of the practice of anesthesiology from clinical genetics and genome-based medicine. Schwinn believes that this divide arose from how traditional anesthesiology is done "in the trenches" as compared to genetics.

"I think anesthesia is really the last physiology lab in medicine," she says, meaning that it gives physicians a chance to see, live and in real time, the human body pushed to the limit. "But what we don't have in anesthesiology is the opportunity to study families the way one would in traditional genetics. Rather, we have populations of patients coming to the hospital for certain procedures. Of course, the beauty is that that's medicine in practice! What we see everyday and what we diagnose are simply patients walking in with symptoms."

A subset of those patients eventually makes up the pool of 45,000 anesthesias that are performed at Duke every year. Schwinn emphasizes that while traditional family studies may be impractical within this pool, Duke anesthesia patients nevertheless comprise a large database for case-control studies of intraoperative outcomes, especially those undergoing heart surgery or those in premature labor. To study these outcomes, Schwinn has assembled a team of statistical geneticists, clinicians and molecular pharmacologists in order to define relevant genetic variants.

Already, instances of polymorphisms useful in the operating room are beginning to crop up in the literature. For example, in the gene for factor V Leiden, a common coagulation factor, a polymorphism has been found that appears to protect against blood loss after cardiac surgery. Elsewhere, recent studies indicate polymorphisms in cardiac potassium channel genes can mediate exceptional and unpredictable arrhythmias in response to even small doses of certain antibiotics, a situation that can prove to be life-threatening in the operating room.

According to Schwinn and a growing contingent of forward-thinking anesthesiologists, the tools of perioperative genomics may soon be a standard part of the operating-room arsenal used to ensure patient safety.

Despite the excitement surrounding these results, even pro-genome anesthesiologists such as Schwinn sound notes of caution, emphasizing that gene association studies do not prove causality. Because such studies are often undertaken across different populations, spurious associations can be found that do not hold up under further scrutiny. Differing genetic backgrounds and environmental factors can skew results all too easily. In an editorial that appeared last year, Schwinn and Assistant Professor of Anesthesiology John Booth took pains to lay out standards for future genetic association studies in perioperative genomics. These standards include: studying large sample populations; careful population screening that uses well-defined clinical end points; taking multiple biochemical measurements where appropriate; and installing rigorous quality control in order to ensure accurate genotyping.

Schwinn stresses the importance of appropriate statistical expertise while noting this is not an issue at Duke. "It's very important to have people analyzing clinical data who really know what they're doing in terms of statistical genetics. And I think the folks here all understand the value of integrating the clinical departments with people who have those skills."

Looking ahead, Schwinn marvels at the untapped potential of perioperative genomics if it is done right. "If we are both careful and visionary, these types of studies can help us predict perioperative outcomes based on preoperative genomic information. They could truly revolutionize clinical research."

The **Tuesday** Series

A seminar series sponsored by the University Program in Genetics and Genomics (UPGG) and the Institute for Genome Sciences & Policy. All seminars take place at 12:30 p.m. in Room 147 of the Nanaline Duke Building.

November

25 **NO SEMINAR**—Thanksgiving Week

December

2 **Mike Grunstein**, *UCLA*
Novel Functions for Histone Deacetylases in Yeast

9 **Anthony Hyman**, *EMBL*
Dynamics of Spindle Assembly in C. elegans Embryos

January

13 **TBA**

20 **Ken Wolfe**, Dept. of Genetics, *Univ. of Dublin, Ireland*
Gene Order Evolution and Birth of a Metabolic Gene Cluster in Yeast

27 **TBA**

February

3 **Mark Johnston**, *Washington Univ., St. Louis*
Millions of Years of Evolution Reveal Functional Features in the Yeast Genome

GenomeLIFE, the newsletter of the Duke Institute for Genome Sciences & Policy, is published monthly and edited by Misha Angrist and Denise Haviland. We welcome your input! Please direct all inquiries, suggestions, and ideas to genomelife@genome.duke.edu

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